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## CLINICAL SCIENCE

# A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial

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**ABSTRACT**

**Objectives** To compare efficacy and safety of ixekizumab (IXE) to adalimumab (ADA) in biological disease-modifying antirheumatic drug-naïve patients with both active psoriatic arthritis (PsA) and skin disease and inadequate response to conventional synthetic disease-modifying antirheumatic drug (csDMARDs).

**Methods** Patients with active PsA were randomised (1:1) to approved dosing of IXE or ADA in an open-label, head-to-head, blinded assessor clinical trial. The primary objective was to evaluate whether IXE was superior to ADA at week 24 for simultaneous achievement of a  $\geq 50\%$  improvement from baseline in the American College of Rheumatology criteria (ACR50) and a 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI100). Major secondary objectives, also at week 24, were to evaluate whether IXE was: (1) non-inferior to ADA for achievement of ACR50 and (2) superior to ADA for PASI100 response. Additional PsA, skin, treat-to-target and quality-of-life outcome measures were assessed at week 24.

**Results** The primary efficacy endpoint was met (IXE: 36%, ADA: 28%;  $p=0.036$ ). IXE was non-inferior for ACR50 response (IXE: 51%, ADA: 47%; treatment difference: 3.9%) and superior for PASI100 response (IXE: 60%, ADA: 47%;  $p=0.001$ ). IXE had greater response versus ADA in additional PsA, skin, nail, treat-to-target and quality-of-life outcomes. Serious adverse events were reported in 8.5% (ADA) and 3.5% (IXE) of patients.

**Conclusions** IXE was superior to ADA in achievement of simultaneous improvement of joint and skin disease (ACR50 and PASI100) in patients with PsA and inadequate response to csDMARDs. Safety and tolerability for both biologicals were aligned with established safety profiles.

**INTRODUCTION**

The goal of treatment in patients with active psoriatic arthritis (PsA) is to simultaneously improve the manifestations of the disease, including arthritis and skin disease. Improvements in both joint and skin disease are necessary to achieve optimal improvement in health-related quality of life in patients

**Key messages****What is already known about this subject?**

- ▶ Many patients with psoriatic arthritis and active skin and joint disease do not achieve satisfactory clinical response with conventional synthetic disease-modifying antirheumatic therapy in both important domains of the disease simultaneously.
- ▶ In this patient group, biological disease-modifying antirheumatic drugs (bDMARDs) offer additional treatment options, but the comparative efficacy and safety of bDMARDs is not known.

**What does this study add?**

- ▶ The findings of this study demonstrate that ixekizumab was superior to adalimumab for simultaneous achievement of American College of Rheumatology 50 (ACR50) and Psoriasis Area and Severity Index (PASI100), was non-inferior to adalimumab for achievement of ACR50 and was superior to adalimumab for achievement of PASI100 at week 24.
- ▶ Response with ixekizumab was significantly greater than adalimumab for Minimal Disease Activity, Very Low Disease Activity, Disease Activity in Psoriatic Arthritis remission ( $\leq 4$ ), change from baseline in modified Composite Psoriatic Disease Activity Index, resolution of enthesitis (Spondyloarthritis Research Consortium of Canada Enthesitis Index=0), PASI75, PASI90 and Dermatology Life Quality Index (0 or 1) and was at least similar to adalimumab for all other psoriatic arthritis, treat-to-target, skin, nail and quality of life endpoints.

**How might this impact on clinical practice or future developments?**

- ▶ The findings of this study increase awareness of current treatment options and informs evidence-based treatment decisions for patients with active psoriatic arthritis and active psoriatic skin disease.



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with PsA, an important indicator of treatment success.<sup>1</sup> Treatment options for patients with PsA include non-pharmacological intervention, symptomatic treatment, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs) and other immunomodulatory therapies.<sup>2-6</sup>

Among patients who fail to achieve adequate response to csDMARDs, bDMARDs targeting inflammatory cytokines such as tumour necrosis factor  $\alpha$  (TNF), interleukin (IL)-12/23 or IL-17A offer an alternative either as a combination therapy with csDMARDs or as monotherapy. Some evidence suggests that combination therapy with csDMARDs such as methotrexate may inhibit development of antidrug antibodies to bDMARDs, and some studies observed better treatment persistence with combination therapy.<sup>7</sup> Concomitant methotrexate has been associated with greater serum concentration of adalimumab (ADA) versus patients receiving ADA monotherapy.<sup>8</sup>

The objective of the current study is to determine whether ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, is superior to ADA, a TNF inhibitor, as measured by a combined arthritis and skin endpoint in bDMARD-naïve patients with active PsA and inadequate response to csDMARDs. Concomitant use of a stable dose of csDMARDs was permitted during the study.

## METHODS

### Participants

Eligible participants had an established diagnosis of PsA for at least 6 months, fulfilled the Classification for Psoriatic Arthritis criteria with at least 3/66 swollen and 3/68 tender joints, had previous inadequate response to  $\geq 1$  csDMARD, had active plaque psoriasis affecting  $\geq 3\%$  of body surface area (BSA) and had not previously received bDMARD or Janus kinase inhibitor therapy.<sup>9</sup> Patients on csDMARDs at screening were allowed to continue a stable dose of csDMARD therapy.

### Study design

This study is a 52 week, phase IIIb/IV, multicentre, randomised, open-label, blinded-assessor, parallel-group study evaluating the efficacy and safety of IXE versus ADA in bDMARD-naïve, csDMARD-inadequate-responder patients (based on medical history) with active PsA. Following a 28-day screening period, participants were randomised 1:1 to open-label IXE or ADA during a 52-week open-label treatment period (weeks 0–52). Randomisation was stratified by concomitant csDMARD use at baseline and moderate-to-severe plaque psoriasis involvement (Psoriasis Area and Severity Index (PASI)  $\geq 12$ , BSA  $\geq 10\%$  and static physician's global assessment (sPGA)  $\geq 3$ ). Study visits occurred at screening, baseline and postbaseline at weeks 1, 4, 8, 12, 16, 24, 32, 40 and 52. Treatment allocation was revealed after randomisation to sponsors, investigators, patients and all study staff except for blinded assessors. Blinded assessors evaluated tender joint count, swollen joint count, PASI, % BSA, enthesitis, Leeds Dactylitis Index–Basic (LDI-B), Nail Psoriasis Severity Index (NAPSI) fingernails and sPGA.

Participants received approved-label dosing of assigned treatments by subcutaneous injection. All patients randomised to IXE received a 160 mg starting dose (two 80 mg injections) at week 0. IXE-treated patients received 80 mg IXE every 4 weeks from week 4 onwards (seven doses up to week 24) unless they met criteria for moderate-to-severe psoriasis, in which case they received 80 mg IXE every 2 weeks from week 2 to week 12, followed by IXE every 4 weeks (10 doses up to week 24, three

additional doses). Patients randomised to ADA received a 40 mg starting dose followed by 40 mg ADA every 2 weeks starting at week 2 (12 doses up to week 24), or if they met criteria for moderate-to-severe psoriasis, they received an 80 mg starting dose of ADA (two 40 mg injections) at week 0, followed by 40 mg ADA every 2 weeks starting at week 1 (14 doses up to week 24, two additional doses). Thus, among patients with moderate-to-severe psoriasis, the IXE dosing regimen resulted in one more additional dose relative to those receiving ADA.

SPRIT-H2H (Clinicaltrials.gov: NCT03151551) was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, and the study protocol was approved by the ethical review board prior to the start of study-related procedures.

### Patient and public involvement

Patients were not involved in the design or conduct of the study, development of outcomes or dissemination of study results.

### Efficacy endpoints

The primary and two major secondary endpoints were tested using a sequential hierarchical testing procedure in the order presented below. There were no adjustments for multiple comparisons for any other analyses.

#### Primary endpoint (simultaneous achievement of ACR50 and PASI100)

The primary endpoint assessed superiority of IXE versus ADA at week 24, as measured by the proportion of patients who simultaneously achieved an American College of Rheumatology 50 (ACR50) response and PASI100 response. After the week 24 database lock and initial analysis run, a medical inconsistency in baseline PASI data was identified (PASI=0 but BSA  $\geq 3\%$ ) in nine patients. This scenario was not anticipated or described in the protocol or statistical analysis plan. The inconsistency was resolved using medical judgement. The impacted patients met baseline criteria for active psoriasis. In the final primary analysis, patients with baseline PASI=0 and BSA  $\geq 3$  were considered PASI100 responders if, and only if, an absolute PASI=0 and BSA=0 was achieved at week 24. Multiple analyses to assess the robustness of this approach were conducted (see online supplementary table 1).

#### Major secondary endpoint 1 (ACR50)

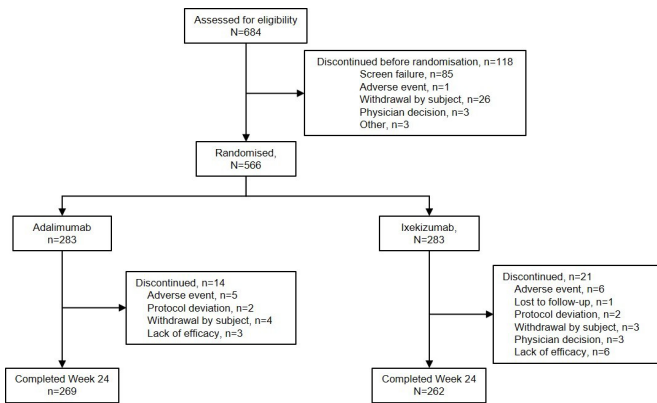
Major secondary endpoint 1 assessed whether IXE was non-inferior to ADA at week 24 as measured by the proportion of patients achieving ACR50.

#### Major secondary endpoint 2 (PASI100)

Major secondary endpoint 2 assessed whether IXE was superior to ADA at week 24 as measured by the proportion of patients achieving PASI100.

### Other secondary endpoints

Additional prespecified outcomes included the proportion of patients achieving  $\geq 20\%$  or  $\geq 70\%$  improvement from baseline in ACR criteria (ACR20/70),  $\geq 75\%$  or  $\geq 90\%$  improvement from baseline in PASI (PASI75/90), resolution of fingernail psoriasis (NAPSI fingernails=0), PsA minimal disease activity (MDA), a minimal clinically important difference (MCID) of  $\geq 0.35$ -point improvement from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) among patients with  $\geq 0.35$  at baseline, a Dermatology Life Quality Index score of



**Figure 1** Participant flow diagram up to week 24.

0 or 1 (DLQI (0 or 1)), resolution of enthesitis as measured by the Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC Enthesitis Index=0) or Leeds Enthesitis Index (LEI=0) among patients with enthesitis at baseline (SPARCC Enthesitis Index >0 or LEI >0) and resolution of dactylitis as measured by the Leeds Dactylitis Index–Basic (LDI-B=0) among patients with dactylitis at baseline (LDI-B >0). Prespecified continuous outcomes included the mean change from baseline in NAPS1 and the modified Composite Psoriatic Disease Activity Index (mCPDAI) (see online supplementary table 2).

Post hoc continuous analyses included mean change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) and in the psoriatic arthritis disease activity score (PASDAS). Post hoc categorical analyses included the percentage of patients achieving DAPSA  $\leq 4$  (remission), DAPSA  $\leq 14$  (low disease activity or remission), PASDAS  $\leq 3.2$  (low disease activity), PASDAS  $\leq 1.9$  (near remission) and meeting 7/7 MDA criteria (very low disease activity (VLDA)).

### Safety

Treatment-emergent adverse events (TEAEs) were defined as events that first occurred or worsened in severity after the first dose of study treatment and on or prior to the date of the last visit within the treatment period. AEs of special interest included infections, injection-site reactions, cytopaenias, liver function test changes/enzyme elevations, allergic reactions/hypersensitivity, cerebrocardiovascular events, malignancies, depression and suicide/self-injury, interstitial lung disease and inflammatory bowel disease (IBD). Data relating to cerebrocardiovascular events and suspected IBD were adjudicated by external clinical events committees.

### Statistical analyses

Analyses of efficacy were performed at the week 24 primary database lock for the intent-to-treat population, consisting of all randomised patients according to treatment assigned at week 0. A hierarchical multiple testing procedure for the primary and two major secondary endpoints was implemented to control the family-wise type I error rate at a two-sided  $\alpha$  level of 0.05. The first test in the statistical hierarchy was a superiority test of the primary endpoint (simultaneous ACR50 and PASI100). If IXE was determined to be statistically superior to ADA for the primary endpoint, a non-inferiority test of IXE versus ADA was performed for secondary endpoint 1 (ACR50). If the test for major secondary endpoint 1 was successful (indicating IXE was non-inferior to ADA for achieving ACR50 at Week 24), a superiority test was conducted for major secondary endpoint 2

(PASI100). If a test in this sequence was not successful, all subsequent tests were considered unsuccessful.

A fixed-margin approach was used for non-inferiority testing of ACR50 response, where IXE was deemed non-inferior to ADA if the lower bound of the two-sided 95% CI for the difference in proportions of ACR50 responders on IXE minus ADA was greater than the prespecified margin of  $-12.0\%$ . This non-inferiority margin represents an approximately 50% preservation of the ADA treatment effect observed in historical phase III studies per Food and Drug Administration (FDA)/European Medicines Agency (EMA) non-inferiority study design guidelines.<sup>10–13</sup>

Categorical efficacy and health outcome variables were analysed based on treatment success/failure using a logistic regression model with treatment, concomitant csDMARD use at baseline and moderate-to-severe plaque psoriasis involvement as factors. Patients were considered treatment failures (or non-responders) if they did not meet the clinical response criteria or had missing clinical response data at a particular time point of analysis.

Continuous variables were analysed using a mixed effects model of repeated measures analysis, which included treatment group, concomitant csDMARD use at baseline, moderate-to-severe plaque psoriasis involvement and visit as fixed factors; baseline value as covariate; and baseline-by-visit and treatment-by-visit interaction terms. Missing data were imputed using a modified baseline observation carried forward method.

Descriptive safety analyses were performed on all randomised patients according to assigned treatment who received  $\geq 1$  dose of study treatment and included all data available up to the time of database lock.

## RESULTS

### Participants

Of 684 patients screened, 566 were randomised between 24 August 2017 and 24 May 2018, to either ADA (n=283) or IXE (n=283); 269 (95%) patients randomised to ADA and 262 (93%) patients randomised to IXE completed the week 24 study visit (figure 1). Baseline demographics and disease characteristics were balanced between treatment groups (table 1). All patients had active plaque psoriasis with BSA  $\geq 3\%$ .

### Efficacy

Efficacy outcomes at week 24 are summarised in table 2. The primary and all major secondary endpoints of the study were met. The proportion of patients simultaneously achieving ACR50 and PASI100 was significantly ( $p=0.036$ ) greater for patients receiving IXE (36%) than ADA (28%); significant differences were observed as early as week 8 (figure 2A). IXE was non-inferior to ADA as measured by ACR50 response (IXE: 50.5%, ADA: 46.6%, IXE vs ADA treatment difference: 3.9% (95% CI  $-4.3\%$  to  $12.1\%$ )); there were no statistically significant differences in ACR50 response between treatment arms (figure 2B). PASI100 response was significantly ( $p=0.001$ ) greater in the IXE (60%) versus ADA (47%) group; statistically significant differences were observed as early as the first PASI assessment (week 4) and persisted through week 24 (figure 2c).

Significantly more patients achieved PsA MDA (treatment difference: 12.4%, 95% CI 4.3% to 20.4%) and VLDA (treatment difference: 7.1%, 95% CI 1.4% to 12.7%) at week 24 in the IXE versus ADA groups (figure 3A,B). Although there were no significant differences between treatment groups in DAPSA change from baseline (treatment difference:  $-1.64$ , 95% CI  $-3.94$  to  $0.66$ ) or DAPSA low disease activity, including remission (DAPSA  $\leq 14$ ) (treatment difference: 1.1%, 95% CI  $-7.0\%$

**Table 1** Baseline demographics and disease characteristics

	IXE (n=283)	ADA (n=283)
<b>Baseline demographics</b>		
Age, years	47.5 (12.0)	48.3 (12.3)
<b>Sex, n (%)</b>		
Male	162 (57)	150 (53)
Female	121 (43)	133 (47)
<b>Race, n (%)</b>		
White	222 (78)	211 (75)
Asian	29 (10)	33 (12)
Weight, kg	85.3 (19.8)	81.9 (18.3)
Body mass index, kg/m <sup>2</sup>	30.0 (6.9)	29.7 (8.3)
Duration of symptoms since PsA diagnosis, years	6.6 (7.4)	5.9 (6.4)
Duration of symptoms since psoriasis diagnosis, years	16.1 (13.1)	14.7 (12.6)
<b>Concomitant csDMARD use, n (%)</b>		
Concomitant methotrexate use, n (%)	193 (68)	199 (70)
<b>Concomitant methotrexate use, n (%)</b>		
Concomitant methotrexate use, n (%)	167 (59)	169 (60)
<b>Baseline disease scores</b>		
Tender joint count	19.1 (12.7)	21.3 (15.4)
Swollen joint count	10.1 (7.5)	10.7 (8.1)
Patient pain VAS	59.7 (21.9)	62.4 (21.1)
Patient's global assessment of disease activity VAS, mm	62.4 (20.3)	65.2 (20.7)
Physician's global assessment of disease activity VAS, mm	58.9 (17.5)	59.4 (18.2)
HAQ-DI	1.2 (0.6)	1.3 (0.7)
C-reactive protein, mg/L	9.8 (13.7)	10.5 (19.3)
<b>SPARCC Enthesitis Index &gt;0, n (%)</b>		
SPARCC Enthesitis Index*	189 (67)	171 (60)
SPARCC Enthesitis Index*	4.9 (3.5)	5.7 (3.8)
<b>LEI &gt;0, n (%)</b>		
LEI†	159 (56)	147 (52)
LEI†	2.5 (1.4)	2.7 (1.5)
<b>LDI-B &gt;0, n (%)</b>		
LDI-B‡	42 (15)	58 (21)
LDI-B‡	40.1 (42.4)	55.8 (128.4)
<b>PASDAS</b>		
PASDAS	5.8 (0.9)	5.8 (1.0)
<b>DAPSA</b>		
DAPSA	42.7 (20.6)	45.8 (23.5)
<b>Moderate-to-severe psoriasis, n (%)</b>		
PASI ≥12, n (%)	49 (17)	51 (18)
PASI ≥12, n (%)	55 (19)	57 (20)
<b>sPGA ≥3, n (%)</b>		
sPGA ≥3, n (%)	173 (61)	181 (64)
<b>BSA ≥3%, n (%)</b>		
BSA ≥3%, n (%)	283 (100)	283 (100)
<b>BSA ≥10%, n (%)</b>		
BSA ≥10%, n (%)	113 (40)	104 (37)
PASI	7.9 (8.7)	7.7 (7.3)
Percentage BSA	14.8 (18.4)	12.9 (15.6)
DLQI	9.8 (7.6)	9.8 (7.6)
<b>NAPSI fingernails &gt;0, n (%)</b>		
NAPSI fingernails§	191 (68)	177 (63)
NAPSI fingernails§	19.7 (18.5)	19.1 (16.3)

Unless indicated otherwise, data are presented as mean (SD).

\*Assessed in patients with SPARCC Enthesitis Index >0 at baseline.

†Assessed in patients with LEI >0 at baseline.

‡Assessed in patients with LDI-B >0 at baseline.

§Assessed in patients with NAPSI >0 at baseline.

ADA, adalimumab; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; IXE, ixekizumab; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; NAPSI, Nail Psoriasis Area and Severity Index; PASDAS, psoriatic arthritis disease activity score; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; sPGA, static physician's global assessment; VAS, visual analogue scale.

to 9.1%) at week 24 (figure 3C), significantly more patients achieved the more stringent DAPSA remission (DAPSA ≤4) in the IXE versus ADA group (treatment difference: 8.5%, 95% CI

1.7% to 15.3%) (figure 3D). There were no significant differences between treatment groups in PASDAS change from baseline (treatment difference: -0.14, 95% CI -0.38 to 0.10) or PASDAS low disease activity (PASDAS ≤3.2) (treatment difference: 6.0%, 95% CI -2.2% to 14.2%), but PASDAS near remission (PASDAS ≤1.9) was achieved by significantly more patients in the IXE than ADA group (treatment difference: 9.5%, 95% CI 2.5% to 16.6%). No significant differences were observed in ACR20 (treatment difference: -3.2%, 95% CI -10.7% to 4.3%) or ACR70 (treatment difference: 6.0%, 95% CI -1.4% to 13.5%). Change from baseline in mCPDAI was significantly greater in the IXE versus ADA group at week 24 (treatment difference: -0.53, 95% CI -0.85 to -0.20), with statistically significant improvements as early as the first assessment at week 12.

SPARCC Enthesitis Index=0 was achieved by significantly more patients in the IXE versus ADA group at week 24 (treatment difference: 11.6%, 95% CI 1.3% to 21.9%). Both IXE and ADA were efficacious as measured by LDI-B=0 response, but there were no statistically significant differences between treatment groups in LDI-B=0 response up to week 24 (treatment difference: -5.0%, 95% CI -16.8% to 6.8%).

Significantly more patients achieved PASI75 (treatment difference: 11.3%, 95% CI 4.2% to 18.4%) and PASI90 (treatment difference: 15.9%, 95% CI 8.1% to 23.7%) in the IXE versus ADA group. Significant differences in PASI75 and PASI90 response were observed as early as the first assessment at week 4. No significant differences were observed in NAPSI fingernails=0 response between treatment groups (treatment difference: 8.4%, 95% CI -1.8% to 18.6%). However, NAPSI fingernails change from baseline was significantly greater with IXE than ADA at week 24 (treatment difference: -3.37, 95% CI -5.40 to -1.33), with significant improvements as early as the first assessment at week 12.

DLQI (0, 1) response was significantly greater at week 24 in the IXE versus ADA group (treatment difference: 9.5%, 95% CI 1.4% to 17.7%), with significant differences as early as the first assessment at week 4. There were no statistically significant differences between groups in HAQ-DI MCID response (treatment difference: 1.3%, 95% CI -6.9% to 9.6%).

### Safety

TEAEs were more common in the IXE versus ADA group (table 3); most were mild or moderate in severity. Discontinuations due to AEs and serious AEs (SAEs) were numerically lower in the IXE versus ADA group. No deaths occurred during the study.

Safety data were analysed in the safety population at the time of database lock. Of the 566 randomised patients, n=70 completed, n=52 discontinued and n=444 were ongoing in the open-label treatment period at the time of database lock.

Most infection-related TEAEs were mild or moderate in severity. Serious infections were more frequent in the ADA versus IXE group (see online supplementary table 3). Three patients discontinued due to infection-related AEs, including two in the ADA group (lymph node tuberculosis, pneumonia legionella) and one in the IXE group (arthritis bacterial). There were no confirmed cases of pulmonary tuberculosis. TEAEs of *Candida* infections were more frequent in the IXE group (n=7; four oral and three genital *Candida* infections) than the ADA group (n=2; one oral and one genital *Candida* infection). All *Candida*-related TEAEs resolved except one (IXE, oral *Candida*) that was ongoing at the week 24 database lock; none resulted in discontinuation.

**Table 2** Efficacy and health outcomes at week 24

	IXE (n=283)	ADA (n=283)	Treatment difference IXE versus ADA (95% CI)	IXE versus ADA P value
<b>Primary endpoint</b>				
ACR50+PASI100	102/283 (36.0) 30.4% to 41.6%	79/283 (27.9) 22.7% to 33.1%	8.1% (0.5% to 15.8%)	0.036
<b>Major secondary endpoints</b>				
ACR50*	143/283 (50.5) 44.7% to 56.4%	132/283 (46.6) 40.8% to 52.5%	3.9% (-4.3% to 12.1%)	0.338
PASI100	170/283 (60.1) 54.4% to 65.8%	132/283 (46.6) 40.8% to 52.5%	13.4% (5.3% to 21.6%)	0.001
<b>PsA endpoints</b>				
MDA	135/283 (47.7) 41.9% to 53.5%	100/283 (35.3) 29.8% to 40.9%	12.4% (4.3% to 20.4%)	0.003
VLDA†	49/283 (17.3) 12.9% to 21.7%	29/283 (10.2) 6.7% to 13.8%	7.1% (1.4% to 12.7%)	0.015
DAPSA remission (≤4)†	75/283 (26.5) 21.4% to 31.6%	51/283 (18.0) 13.5% to 22.5%	8.5% (1.7% to 15.3%)	0.016
DAPSA low disease activity or remission (≤14)†	174/283 (61.5) 55.8% to 67.2%	171/283 (60.4) 54.7% to 66.1%	1.1% (-7.0% to 9.1%)	0.737
DAPSA, LSM change from baseline (SE)†	-31.74 (0.94)	-30.10 (0.94)	-1.64 (-3.94 to 0.66)	0.161
PASDAS low disease activity (≤3.2)†	164/283 (58.0) 52.2% to 63.7%	147/283 (51.9) 46.1% to 57.8%	6.0% (-2.2% to 14.2%)	0.153
PASDAS near remission (≤1.9)†	82/283 (29.0) 23.7% to 34.3%	55/283 (19.4) 14.8% to 24.0%	9.5% (2.5% to 16.6%)	0.009
PASDAS, LSM change from baseline (SE)†	-3.08 (0.10)	-2.94 (0.10)	-0.14 (-0.38 to 0.10)	0.260
mCPDAI, LSM change from baseline (SE)	-3.98 (0.14)	-3.46 (0.13)	-0.53 (-0.85 to -0.20)	0.002
ACR20	195/283 (68.9) 63.5% to 74.3%	204/283 (72.1) 66.9% to 77.3%	-3.2% (-10.7% to 4.3%)	0.403
ACR70	90/283 (31.8) 26.4% to 37.2%	73/283 (25.8) 20.7% to 30.9%	6.0% (-1.4% to 13.5%)	0.111
SPARCC Enthesitis Index=0‡	107/189 (56.6) 49.5% to 63.7%	77/171 (45.0) 37.6% to 52.5%	11.6% (1.3% to 21.9%)	0.019
LEI=0§	95/159 (59.7) 52.1% to 67.4%	81/147 (55.1) 47.1% to 63.1%	4.6% (-6.4% to 15.7%)	0.432
LDI-B=0¶	37/42 (88.1) 78.3% to 97.9%	54/58 (93.1) 86.6% to 99.6%	-5.0% (-16.8% to 6.8%)	0.658
<b>Skin and nail psoriasis endpoints</b>				
PASI75	227/283 (80.2) 75.6% to 84.9%	195/283 (68.9) 63.5% to 74.3%	11.3% (4.2% to 18.4%)	0.002
PASI90	203/283 (71.7) 66.5% to 77.0%	158/283 (55.8) 50.0% to 61.6%	15.9% (8.1% to 23.7%)	<0.001
NAPSI fingernails=0**	111/191 (58.1) 51.1% to 65.1%	88/177 (49.7) 42.4% to 57.1%	8.4% (-1.8% to 18.6%)	0.082
NAPSI, LSM change from baseline (SE)	-15.89 (0.82)	-12.53 (0.82)	-3.37 (-5.40 to -1.33)	0.001
<b>Quality of life endpoints</b>				
HAQ-DI ≥0.35††	168/252 (66.7) 60.8% to 72.5%	166/254 (65.4) 59.5% to 71.2%	1.3% (-6.9% to 9.6%)	0.741
DLQI (0, 1)	174/283 (61.5) 55.8% to 67.2%	147/283 (51.9) 46.1% to 57.8%	9.5% (1.4% to 17.7%)	0.020

Unless otherwise indicated, values are presented as n/N (%), 95% CI.

\*The treatment difference of IXE minus ADA was 3.9% (95% CI -4.3% to 12.1%). The lower bound of the 95% CI (-4.3%) was greater than -12%, thus meeting noninferiority criteria.

†Post hoc analysis.

‡Assessed for patients with SPARCC Enthesitis Index score >0 at baseline.

§Assessed for patients with LEI score >0 at baseline.

¶Assessed for patients with LDI-B score >0 at baseline.

\*\*Assessed for patients with NAPSI fingernails score >0 at baseline.

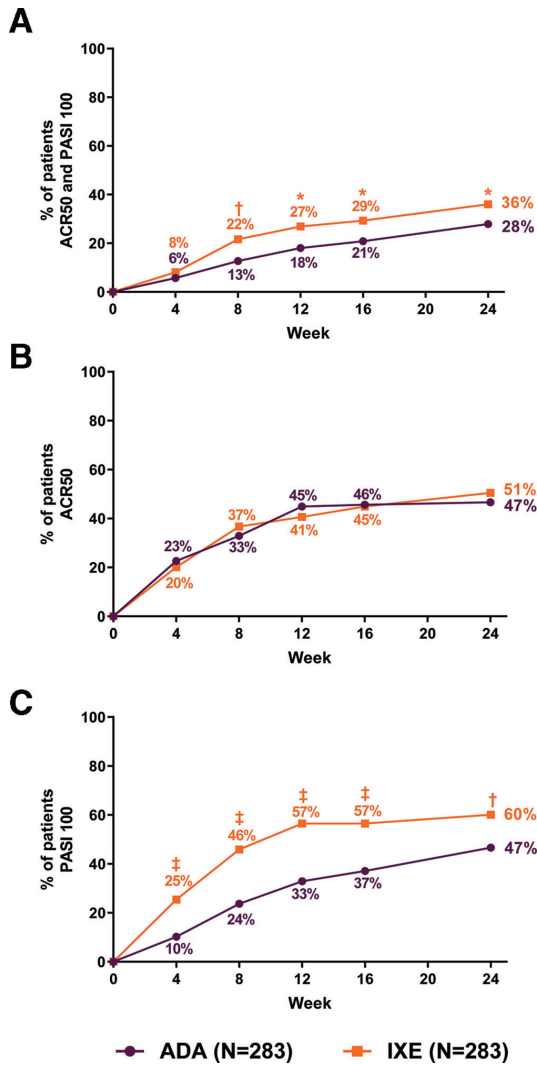
††Assessed for patients with HAQ-DI score ≥0.35 at baseline. A response of ≥0.35 change from baseline is the minimal clinically important difference in HAQ-DI.

ACR, American College of Rheumatology; ADA, adalimumab; DAPSA, Disease Activity in Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; IXE, ixekizumab; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; LSM, least squares mean; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; NAPSI, Nail Psoriasis Area and Severity Index; PASDAS, psoriatic arthritis disease activity score; PASI, Psoriasis Area and Severity Index; SPARCC, Spondyloarthritis Research Consortium of Canada; VLDA, very low disease activity.

Injection-site reactions were more frequent in the IXE versus ADA group; most were mild in severity. One severe injection-site reaction (injection site hypersensitivity) occurred in the ADA group, and one SAE (injection-site rash) occurred in the IXE group. Discontinuations due to injection-site reactions occurred in one IXE-treated and three ADA-treated patients. Most treatment-emergent allergic/hypersensitivity events were mild or

moderate in severity, all were nonanaphylactic and none were SAEs. One ADA-treated patient discontinued due to an allergic/hypersensitivity event (hypersensitivity).

One serious treatment-emergent cerebrocardiovascular event occurred in each treatment group (IXE: atrial fibrillation; ADA: myocardial ischaemia). One IXE-treated patient discontinued due to a treatment-emergent cerebrocardiovascular

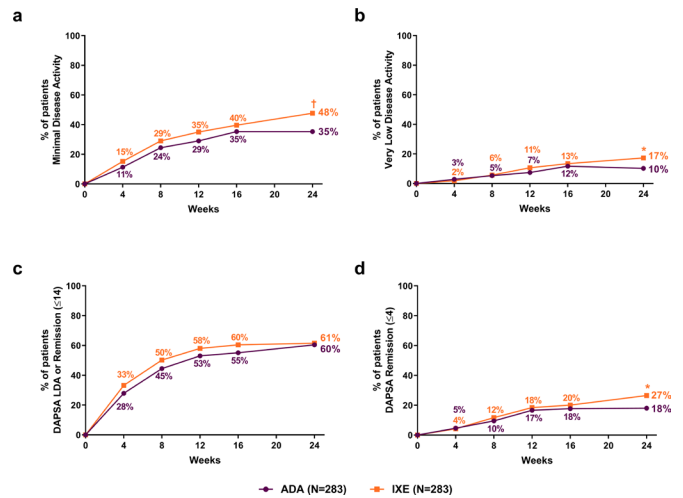


**Figure 2** Clinical response rates for primary and major secondary outcomes through week 24 (non-responder imputation). (A) Percentage of patients simultaneously achieving ACR50 and PASI100 (primary endpoint). (B) Percentage of patients achieving ACR50 (major secondary endpoint). The treatment difference of IXE minus ADA was 3.9% (95% CI -4.3% to 12.1%). The lower bound of the 95% CI (-4.3%) was greater than -12%, thus meeting noninferiority criteria. (C) Percentage of patients achieving PASI100. IXE versus ADA: \*P<0.05, †p<0.01, ‡p<0.001. ACR, American College of Rheumatology; ADA, adalimumab; IXE, ixekizumab; PASI, Psoriasis Area Severity Index.

event of bradycardia. One major adverse cerebrocardiovascular event of moderate haemorrhagic stroke occurred in the ADA group; this event was an SAE and did not result in discontinuation.

No treatment-emergent malignancies occurred in the IXE group, and three occurred in the ADA group, two of which were considered by the investigator as SAEs (basal cell carcinoma and rectal neoplasm). No patients discontinued due to malignancy. No TEAEs of cytopenia were SAEs, and none resulted in discontinuation. No patients had a worsening to grade 3 or 4 neutropenia. There were no suicide or self-injury-related TEAEs in either group. There were no depression-related SAEs, and no patients discontinued due to depression-related TEAEs.

Suspected IBD-related events were adjudicated by an expert panel as defined by the EPIdemiologique des Maladies de



**Figure 3** Clinical response rates for treat-to-target outcomes through week 24. (A) Percentage of patients achieving minimal disease activity. (B) Percentage of patients achieving very low disease activity. (C) Percentage of patients achieving a DAPSA score of ≤14 (LDA or remission). (D) Percentage of patients achieving a DAPSA score ≤4 (remission). IXE versus ADA: \*P<0.05, †p<0.01, ‡p<0.001. ADA, adalimumab; DAPSA, Disease Activity in Psoriatic Arthritis; IXE, ixekizumab; LDA, low disease activity.

l'Appareil Digestif (EPIMAD) criteria for adjudication of suspected IBD, where 'probable' and 'definite' classifications are considered as confirmed cases.<sup>14</sup> Three TEAEs were identified in two IXE-treated patients as suspected IBD. One IXE-treated patient had an event reported as 'colitis' that was sent for adjudication, but there was insufficient information to make a definitive classification. The same patient also had an event of 'colitis ulcerative', adjudicated as possible ulcerative colitis, which resulted in study discontinuation. Another IXE-treated patient with no prior medical history of IBD had an event reported as 'colitis' that was adjudicated as probable Crohn's disease and was the only case that met EPIMAD criteria for confirmed IBD. No SAEs of IBD occurred, and no TEAEs of potential IBD were reported in the ADA group.

**DISCUSSION**

Treatment choices for PsA in clinical practice are made between medications that have shown efficacy and sufficient safety in clinical trials. Because comparative clinical trials are rare in PsA, indirect comparisons are often made using meta-analyses. However, head-to-head trials where active agents are compared, rather than an active agent and placebo, offer the highest level of evidence.<sup>15-18</sup> The SPIRIT-P1 and OPAL trials (which compared IXE or tofacitinib, respectively, with placebo) included an ADA active reference arm but were not powered for head-to-head comparisons with ADA.<sup>11 19</sup> A study (EXCEED 1) comparing replacement of csDMARDs with secukinumab or adalimumab monotherapy is ongoing (NCT02745080). Although both SPIRIT-H2H and EXCEED 1 included bDMARD-naïve patients with inadequate response to csDMARDs, key differences between the studies include blinding (double-blind in EXCEED 1 vs open-label in SPIRIT-H2H) and concomitant csDMARD use (not allowed in EXCEED 1). SPIRIT-H2H is the first completed head-to-head trial comparing two bDMARDs in patients with active PsA and inadequate response to csDMARDs.

Although skin involvement is usually mild in patients with PsA, clinicians and patients judge the impact of a PsA treatment by

**Table 3** Safety outcomes

	IXE (n=283)	ADA (n=283)
Extent of exposure, mean days (total patient-years)	236.8 (183.5)	228.9 (117.3)
Treatment-emergent adverse events	197 (69.6)	173 (61.1)
Mild	97 (34.3)	87 (30.7)
Moderate	91 (32.2)	71 (25.1)
Severe	9 (3.2)	15 (5.3)
Serious adverse events	10 (3.5)	24 (8.5)
Deaths	0	0
Discontinuations due to adverse events	7 (2.5)	13 (4.6)
Adverse events of special interest		
Infections	102 (36.0)	87 (30.7)
Serious infections	4 (1.4)	8 (2.8)
Candida infections	7 (2.5)	2 (0.7)
Injection-site reactions	27 (9.5)	9 (3.2)
Allergic/hypersensitivity reactions	7 (2.5)	11 (3.9)
Potential anaphylaxis	0	0
Cytopenias	5 (1.8)	11 (3.9)
Cerebrocardiovascular events*	3 (1.1)	5 (1.8)
Malignancies	0	3 (1.1)
Depression	3 (1.1)	7 (2.5)
Inflammatory bowel disease	2 (0.7)†	0
Ulcerative colitis	1 (0.4)‡	0
Crohn's disease	1 (0.4)§	0

Safety data were analysed in the safety population at the time of database lock. Of the 566 randomized patients, n=70 completed, n=52 discontinued, and n=444 were ongoing in the open label treatment period at the time of database lock.

\*Of eight treatment-emergent cerebrocardiovascular events reported, four (IXE: n=2 (0.7%); ADA: n=2 (0.7%)) were adjudicated.

†Epidemiologie des Maladies de l'Appareil Digestif (EPIMAD) criteria for adjudication of suspected inflammatory bowel disease define 'probable' and 'definite' classifications as confirmed cases. Only one case met the EPIMAD criteria of confirmed inflammatory bowel disease.

‡Event was reported as colitis ulcerative and was adjudicated as possible ulcerative colitis.

§Event was reported as colitis and was adjudicated as probable Crohn's disease. ADA, adalimumab; IXE, ixekizumab.

effects on all domains affected by the disease, in particular joints and skin.<sup>20–22</sup> Furthermore, achievement of optimal health-related quality of life, the ultimate treatment goal in PsA, requires improvements in both joint and skin manifestations of the disease.<sup>1</sup> Therefore, a combination of two validated and well-established outcome measures, a relatively stringent endpoint for articular disease (ACR50) and a very stringent endpoint for skin disease (PASI100) was employed as the primary endpoint. The 24-week efficacy data from the present study demonstrate that IXE was superior to ADA in simultaneously leading to an ACR50 and PASI100 response, was non-inferior to ADA for achieving ACR50 and was superior to ADA for achieving PASI100. Furthermore, significantly more patients achieved DAPSA remission (which does not include a measure of skin response) with IXE than ADA, suggesting that skin changes were not the only domain contributing to differences between biologics. IXE further demonstrated significantly higher clinical response rates than ADA at week 24 for SPARCC Enthesitis Index, psoriasis (PASI75/90), fingernail psoriasis (NAPSI fingernails change from baseline), mCPDAI and treat-to-target endpoints of MDA, VLDA and DAPSA remission.<sup>23</sup> Rapid and significantly greater improvements in skin-related quality of life were also observed (DLQI (0 or 1)). No significant differences were observed between treatment

groups for ACR20/50/70, suggesting IXE had similar speed and level of response compared to ADA for joint improvement.

SAEs, especially those related to infections, were numerically higher in the ADA group. Infections were more frequent in the IXE group than the ADA group. Injection site reactions (including injection site pain) were numerically higher in the IXE arm, although most were mild in both groups. Overall, the safety profiles of both bDMARDs were consistent with those described in the prescriber information.

A key strength of the SPIRIT-H2H study is its relevance to real-world clinical settings. The open-label study design and absence of a placebo arm was modelled after real-world clinical settings where patients receive active treatments and are aware of which treatment they receive. Patients were treated with the approved dosing regimens of both IXE and ADA (according to presence/absence of moderate-to-severe psoriasis), as monotherapy or in combination with csDMARDs. Approximately 82% of patients did not meet criteria for moderate-to-severe psoriasis, consistent with the patient population typically seen by rheumatologists.<sup>20–22</sup>

Although comparisons between clinical studies are limited by differences in design and study population, joint and skin responses for both IXE and ADA were higher in SPIRIT-H2H than in historical studies.<sup>10 11 24</sup> The use of two efficacious treatments, open-label study design and lack of a placebo arm may have contributed to increased responses in SPIRIT-H2H, since all patients knew they would receive active therapy. To minimise bias, key outcomes were measured by blinded assessors. However, an expectation of different rates of improvement (especially in skin outcomes) with IXE versus ADA could potentially influence blinded assessors. However, this limitation also exists for double-blind, placebo-controlled studies, where greater response is expected with an active treatment versus a placebo comparator. SPIRIT-H2H is ongoing through 52 weeks of treatment, and the current report is limited to 24 weeks. Thus, it is currently unknown how clinical responses will compare over longer treatment periods. An additional study limitation was the absence of imaging or structural joint damage assessments. Though the patient population in this study is similar to other clinical trials in PsA, it may not represent all patients with PsA in daily clinical practice (eg, patients in this study predominantly had polyarthritis).

In conclusion, IXE was associated with greater improvement of a combined articular and cutaneous endpoint in PsA compared with ADA over a 24-week period and had numerically lower incidence of SAEs compared to ADA.

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a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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## INCLUSION/EXCLUSION CRITERIA

### Inclusion criteria

Patients were eligible to be included in the study only if they met all of the following criteria at screening:

1. Patients with a documented diagnosis of psoriatic arthritis (PsA) for at least 6 months fulfilling the Classification for Psoriatic Arthritis (CASPAR) and the activity of disease as defined by the presence of at least 3 swollen joints (66 joints) and 3 tender joints (68 joints) in patients who were biologic disease-modifying anti-rheumatic drugs (bDMARD) naive. Patients must have had active psoriatic skin lesions (plaque) of plaque psoriasis with a body surface area (BSA) of at least 3% at screening (Visit 1) and randomization (Visit 2).
  1. Were male or female patients 18 years or older
    - a. Male patients agreed to use a reliable method of birth control during the study.
    - b. Female patients who were:
      - i. Women of childbearing potential who tested negative for pregnancy and agreed to use a reliable method of birth control or remained abstinent during the study and for at least 12 weeks after the last dose of investigational product, whichever was longer. Methods of contraception considered acceptable when used properly included oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.
      - ii. Women of nonchildbearing potential, defined as women who had surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation);
- OR



Women who were  $\geq 60$  years of age;

OR

Women who were  $\geq 40$  and  $< 60$  years of age who had a cessation of menses for  $\geq 12$  months and a FSH test confirming nonchildbearing potential ( $\geq 40$  mIU/mL).

2. Had a documented diagnosis of psoriatic arthritis (PsA) for at least 6 months and met the Classification for Psoriatic Arthritis (CASPAR) criteria
3. Had active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints at visit 1 (screening) and visit 2 (week 0)
4. Had active psoriatic skin lesions (plaque psoriasis) with a body surface area (BSA)  $\geq 3\%$  at visit 1 (screening) and visit 2 (week 0)
5. Were biologic disease-modifying antirheumatic drug (bDMARD) naive
6. Had an inadequate response when treated with 1 or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)
7. Had given written informed consent approved by Lilly or its designee and the ethical review board governing the site

#### **Exclusion criteria**

Patients were to be excluded from study enrollment if they met any of the following criteria at screening:

8. Were enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
9. Received any prior treatment with any bDMARD therapy or small molecule for PsA or for psoriasis, including investigational therapies (such as, but not limited to, tumor necrosis factor  $\alpha$  (TNF) inhibitors, interleukin (IL)-1 receptor antagonists, IL-6 inhibitors, anti-IL-12/23p40

therapies, T-cell or B-cell–targeted therapies, or Janus kinase inhibitors)

Exception: Previous treatment of phosphodiesterase type 4 inhibitors was permitted. Treatment with phosphodiesterase type 4 inhibitors must have been discontinued at least 8 weeks before randomization (visit 2).

10. Had previously completed or withdrawn from this study or any other study investigating ixekizumab (IXE) or other IL-17 inhibitors, eg, anti-IL-17 or anti-IL-17 receptor (anti-IL-17R) monoclonal antibodies
11. Had a history of drug-induced psoriasis.
12. Used csDMARDs other than methotrexate, leflunomide, sulfasalazine, or cyclosporine in the 8 weeks prior to randomization (visit 2)
13. Discontinued use of methotrexate, sulfasalazine, or cyclosporine within 12 weeks prior to randomization  
  
If taking methotrexate, leflunomide, sulfasalazine, or cyclosporine, must have been treated for at least 12 weeks prior to randomization (visit 2) and on a stable dose for at least 8 weeks prior to randomization, as follows: oral or parenteral methotrexate, 10 to 25 mg/week; leflunomide, 20 mg/day; sulfasalazine, up to 3 g/day; or cyclosporine, up to 5 mg/kg/day. The dose of these allowed concomitant medications must have remained unchanged during the first 24 weeks of the open-label treatment period unless changes were required for safety issues. Local standard of care was to be followed for concomitant administration of folic acid with methotrexate.
14. Discontinued use of leflunomide within 4 weeks prior to randomization (visit 2) or received leflunomide from 4 to 12 weeks prior to randomization and had not undergone a drug elimination procedure
15. Used oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or used variable doses of any oral corticosteroids, within 4 weeks prior to randomization (visit 2)

16. Received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous (IV) injection within 6 weeks prior to randomization (visit 2), or a parenteral injection of glucocorticosteroids was anticipated during the first 24 weeks of the open-label treatment period
17. Concomitantly used nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, unless the patient was on a stable dose for at least 2 weeks prior to randomization (visit 2)
18. Used any opiate analgesic at average daily doses of >30 mg/day of morphine or its equivalent, or used variable doses of any opiate analgesic, within 6 weeks prior to randomization (visit 2)
19. Received systemic nonbiologic psoriasis therapy other than csDMARDs or corticosteroids as indicated above (including, but not limited to, oral psoralens and ultraviolet A light therapy oral retinoids, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, or 1, 25 dihydroxy vitamin D3 and analogs) or phototherapy (including either oral and topical ultraviolet A, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to randomization (visit 2);  
  
OR  
  
Had topical psoriasis treatment within the previous 2 weeks prior to randomization (visit 2)  
  
Exceptions: Weak-potency (WHO Group 1 classification) topical steroids were permitted.
20. Had plaque psoriasis and could not avoid use of tanning booths for at least 4 weeks prior to randomization (visit 2) and during the study
21. Had a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study
22. Had ever received efalizumab or natalizumab or other agents that target alpha-4-integrin
23. Received a live vaccination within 12 weeks prior to randomization (visit 2), or intended to receive a live vaccination during the course of the study or within 12 weeks of completing

treatment in this study, or had participated in a vaccine clinical study within 12 weeks prior to randomization (visit 2). Investigators should have reviewed the vaccination status of their patients and followed the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

Note: Killed/inactive or subunit vaccines were expected to be safe; however, their efficacy with concomitant IXE treatment is unknown.

24. Received a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to randomization (visit 2), or intend to receive a vaccination with BCG during the course of the study or within 12 months of completing treatment in this study
25. Had a diagnosis of other inflammatory arthritic syndromes such as rheumatoid arthritis, ankylosing spondylitis, reactive arthritis, or enteropathic arthritis
26. Had active Crohn's disease or active ulcerative colitis
27. Had fibromyalgia or other chronic pain condition that would confound evaluation of the patient
28. Had evidence of active vasculitis or uveitis
29. Had surgical treatment of a joint within 8 weeks prior to randomization (visit 2) or required such up to week 24
30. Had any major surgery within 8 weeks prior to randomization (visit 2) or required such during the study that, in the opinion of the investigator and in consultation with the sponsor or its designee, would have posed an unacceptable risk to the patient
31. Had a diagnosis or history of malignant disease within the 5 years prior to randomization (visit 2). Note: Patients with successfully treated basal-cell carcinoma (no more than 3) or squamous-cell carcinoma of the skin (no more than 2) within the 5 years prior to randomization may participate in the study.

32. Presence of significant uncontrolled cerebrocardiovascular events (eg, myocardial infarction [MI], unstable angina, unstable arterial hypertension, moderate-to-severe [NYHA class III/IV] heart failure, or cerebrovascular accident); respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders; abnormal laboratory values; or illicit drug use (including cannabinoids, whether legalized or not) at screening (visit 1) that, in the opinion of the investigator, posed an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data
33. Had a history of uncompensated heart failure, fluid overload, or MI or evidence of new-onset ischemic heart disease or other serious cardiac disease within 12 weeks prior to randomization (visit 2)
34. Presence of significant uncontrolled neuropsychiatric disorder; had recent history (within 30 days prior to screening [visit 1] and any time between screening [visit 1] and randomization [visit 2]) of a suicide attempt; or developed active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the “Suicidal Ideation” portion of the Columbia–Suicide Severity Rating Scale [C-SSRS]) or developed suicide-related behaviors as recorded on the C-SSRS at screening (visit 1) or randomization (visit 2); or were clinically judged by the investigator to be at risk for suicide
35. Had presence or personal history or family history (first-degree relative) of demyelinating disorder
36. Patients who had:
  - a. in the past 12 weeks prior to randomization:
    - i. had a serious infection (eg, pneumonia, cellulitis)
    - ii. had been hospitalized for an infection
    - iii. had received IV antibiotics for an infection

- b. in the past 24 weeks prior to randomization had a serious bone or joint infection
  - c. ever had
    - i. an infection of an artificial joint
    - ii. an infection that occurred with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, active histoplasmosis, or coccidioidomycosis); or had a known immunodeficiency
37. Had a known immunodeficiency or were immunocompromised to an extent such that participation in the study would have posed an unacceptable risk to the patient
38. Had a herpes zoster or any other clinically apparent varicella zoster virus infection within 12 weeks prior to randomization (visit 2)
39. Had evidence or suspicion of active or latent tuberculosis (TB) (refer to section below on chest X-ray and tuberculosis testing for details on determining full TB exclusion criteria)
40. Had any other active or recent infection other than mentioned above within 4 weeks of randomization (visit 2) that, in the opinion of the investigator, would have posed an unacceptable risk to the patient if participating in the study
- Note: These patients were eligible to be rescreened 1 time  $\geq 4$  weeks after documented resolution of symptoms.
41. Had a sitting systolic blood pressure  $>160$  mm Hg or diastolic blood pressure  $>100$  mm Hg.
- Note: Determined by 2 consecutive elevated readings. If an initial sitting blood pressure reading exceeded this limit, the blood pressure may have been repeated once after the patient had rested sitting for  $\geq 10$  minutes. If the repeat value was less than the criterion limits, the second value may have been accepted.
42. Tested positive for human immunodeficiency virus (HIV) serology, ie, positive for human immunodeficiency virus antibody (HIVAb)

43. Had evidence of or tested positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+); OR 2) anti-hepatitis B core antibody (HBcAb+) and were HBV deoxyribonucleic acid (DNA) positive

Note: Patients who were HBsAg- and HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who met these criteria at screening were to be identified by the central laboratory and monitored during the study.

44. Had evidence of or tested positive for hepatitis C virus (HCV). A positive test for HCV is defined as: positive for hepatitis C antibody (anti-HCVAb) and positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).

45. Laboratory tests may not have been repeated unless there was a technical error or clinical reason to believe a result may have been erroneous. Laboratory tests could be repeated a maximum of 1 time, and results must have been received and reviewed prior to randomization (visit 2). For eligibility, the most recent lab panel must not have met any of the following criteria:

- a. Neutrophil count <1500 cells/ $\mu$ L
- b. Lymphocyte count <800 cells/ $\mu$ L
- c. Platelet count <100,000 cells/ $\mu$ L
- d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)
- e. Total white blood cell count <3000 cells/ $\mu$ L
- f. Hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients
- g. Serum creatinine >2.0 mg/dL

- h. Clinical laboratory test results at screening that were outside the normal reference range for the population and were considered clinically significant, per investigator assessment.
- 46. Had any condition or contraindication as addressed in the local labelling for adalimumab (ADA) that would preclude the patient from participation in the study
- 47. Had any other condition that precluded the patient from following and completing the study, in the opinion of the investigator
- 48. Women who were breastfeeding
- 49. Were study site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- 50. Were employees of the sponsor or its designee or employees of third-party organizations involved in the study
- 51. Were concurrently enrolled in or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 4 weeks or a period of at least 5 half-lives of the last administration of the drug, whichever was longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- 52. Were unwilling or unable to comply with the use of a data collection device to directly record data from the patient

#### **Chest X-Ray and Tuberculosis Testing**

X-ray



At visit 1, a posterior-anterior view chest x-ray was to be obtained locally, unless the x-ray or results from a chest x-ray obtained within 6 months before randomization (visit 2) were available. The chest x-ray or results were to be reviewed by the investigator or designee to exclude patients with active TB infection.

#### TB Testing

Patient history of TB test results should have been assessed prior to screening (visit 1). Patients with no TB test results on file: Patients were to be tested at screening. A purified protein derivative (PPD) skin test response of  $\geq 5$  mm induration, between approximately 48 and 72 hours after test application, regardless of BCG vaccination history, were to be considered a positive result. In countries where the QuantiFERON-TB<sup>®</sup> Gold test or T-SPOT.TB test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may have been used instead of the PPD test and was to be performed and read locally. If the QuantiFERON-TB<sup>®</sup> Gold test or the T-SPOT.TB test was indeterminate, 1 retest using the same TB test method was allowed. If the retest was indeterminate, then the patient was to be excluded from the study.

Patients with a positive TB test performed at screening (visit 1) but with no other evidence of active TB were eligible to be rescreened 1 time and enrolled without repeating the TB test based on the following requirements:

- after receiving at least 4 weeks of appropriate latent TB infection therapy
- with no evidence of hepatotoxicity (ALT/AST must remain  $\leq 2$ x ULN) upon retesting of serum ALT/AST prior to randomization (visit 2). Such patients must have completed appropriate latent TB infection therapy during the course of the study to remain eligible.
- met all other inclusion and exclusion criteria for participation

If rescreening occurred within 6 months of the date of the screening chest x-ray, there was no need for repeat of chest x-ray for enrollment consideration.

#### Patients With Negative TB Test Results on File

Patients with documentation of a negative test result within 3 months before randomization (visit 2) should not have been administered a TB test at screening (visit 1). Documentation of PPD test results must have included a record of the size of the induration response; otherwise a retest at screening (visit 1) was required to determine patient eligibility.

#### Patients With Positive TB Test Results on File

Patients with prior history of a positive TB test should not receive a TB test at screening (visit 1). Documentation of this history and of at least 4 weeks of appropriate latent TB treatment prior to randomization (visit 2) was required for study eligibility. Patients who had a documented history of completing an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed and no evidence of active TB were eligible to participate in the study. Patients who had household contact with a person with active TB were to be excluded, unless appropriate and documented prophylaxis for TB was given.

## **SUPPLEMENTARY METHODS**

### **Randomization and Blinding**

Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). Site personnel confirmed the correct investigational product by entering a confirmation number found on the investigational product into the IWRS.

Blinded assessors were not allowed to know patient allocation or to be otherwise involved in study procedures, and patients were instructed not to communicate with blinded assessors except for communication required to conduct the blinded data assessment. A third person from the study site was present during each procedure conducted by the blinded assessor to observe and document that the blinding of the assessor was maintained. If unintentionally unblinded, the blinded assessor was replaced. Blinded assessors were required to have at least 1 year of experience for administering the outcome instruments.

### **List of Study Endpoints**

Primary endpoint:

- Proportion of patients simultaneously achieving American College of Rheumatology criteria (ACR50) and Psoriasis Area and Severity Index (PASI100) at week 24

Major secondary endpoints:

- Proportion of patients achieving ACR50 in each treatment group at week 24
- Proportion of patients achieving PASI100 in each treatment group at week 24

PsA endpoints:

- Proportion of patients achieving ACR20, ACR50, and ACR70 responses
- Change from baseline in individual components of the ACR Core Set: tender joint count (TJC), swollen joint count (SJC), patient's pain assessment, patient's global assessment of disease activity, physician's global assessment of disease activity, C-reactive protein (CRP), and Health Assessment Questionnaire–Disability Index (HAQ-DI) score
- Proportion of patients simultaneously achieving ACR50 and PASI100 response
- Change from baseline in the Disease Activity Score (28 diarthrodial joint count) based on CRP (DAS28-CRP)
- Proportion of patients achieving minimal disease activity (MDA)
- Proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC)
- Change from baseline in modified Composite Psoriatic Disease Activity Index (mCPDAI) score
- Proportion of patients achieving low disease activity or remission according to the mCPDAI definition
- Proportion of patients with HAQ-DI improvement  $\geq 0.35$
- Change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index score in patients with enthesitis at baseline (ie, baseline SPARCC Enthesitis Index score  $>0$ )
- Change from baseline in the Leeds Enthesitis Index (LEI) score in patients with enthesitis at baseline (ie, baseline LEI score  $>0$ )
- Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the SPARCC Enthesitis Index (ie, baseline SPARCC Enthesitis Index score  $>0$ )
- Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the LEI (ie, baseline LEI score  $>0$ )

- Change from baseline in the Leeds Dactylitis Index-Basic (LDI-B) score in patients with dactylitis at baseline (ie, baseline LDI-B score >0)
- Proportion of patients with resolution in dactylitis in the subgroup of patients with dactylitis at baseline as measured by the LDI-B (ie, baseline LDI-B score >0)

Psoriasis/nail endpoints:

- Change from baseline in BSA
- Proportion of patients who achieve the following PASI scores: PASI75, PASI90, or PASI100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively)
- Proportion of patients achieving an absolute PASI score  $\leq 1$  or  $\leq 2$  or  $\leq 3$
- Change from baseline in the Nail Psoriasis Severity Index (NAPSI) fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI fingernails score >0)

Quality of life endpoints:

- Change from baseline in the Itch Numeric Rating Scale (NRS) score
- Proportion of patients with Itch NRS score equal to 0
- Change from baseline in Fatigue Severity NRS score
- Change from baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
  - Physical Component Summary score
  - Mental Component Summary score
- Change from baseline in measures of health utility (European Quality of Life–5 Dimensions 5 Level health outcomes instrument [EQ-5D-5L])
- Change from baseline in Dermatology Life Quality Index (DLQI) total score

- Change from baseline in Treatment Satisfaction Questionnaire

Safety endpoints:

- Change from baseline in C-SSRS

### **Outcome Measures**

ACR20, ACR50, and ACR70 responses are defined as an improvement from baseline of  $\geq 20\%$ ,  $\geq 50\%$ , or  $\geq 70\%$ , respectively, in TJC (68 joints), SJC (66 joints), and at least 3 of the 5 ACR Core Set criteria: patient's assessment of pain (patient pain) visual analog scale (VAS), patient's global assessment of disease activity (PatGA) VAS, physician's global assessment of disease activity (PGA) VAS, patient's assessment of physical function as measured by the HAQ-DI, and CRP. CRP was the ACR Core Set measure of acute-phase reactant and was measured with a high-sensitivity assay at a central laboratory to assess the effect of IXE on the patient's PsA.

Patients were classified as achieving MDA if they fulfilled 5 of 7 of the MDA components (TJC  $\leq 1$ ; SJC  $\leq 1$ ; PASI total score  $\leq 1$  or BSA  $\leq 3$ ; patient pain VAS score  $\leq 15$ ; PatGA VAS score  $\leq 20$ ; HAQ-DI score  $\leq 0.5$ ; and tender enthesal points  $\leq 1$ ). Patients were classified as achieving VLDA if they fulfilled 7 of 7 of the MDA components.

The DAPSA is a composite measure that includes TJC (68 joints) and SJC (66 joints), PatGA VAS, patient pain VAS, and CRP. DAPSA is calculated from the sum of the PatGA and patient pain VAS in centimeters and TJC, SJC, and CRP level in mg/dL. Higher scores reflect more severe disease activity.[1] Patients are classified as achieving DAPSA remission if they achieve a DAPSA score  $\leq 4$  and DAPSA low disease activity or remission if they achieve a DAPSA score  $\leq 14$ .[2]

The PASDAS is a weighted index comprising assessments of joints, function, acute phase response, quality of life, and the PGA VAS and PatGA VAS (0mm to 100mm). The TJC is 68 joints and the SJC is 66 joints. The score range of the PASDAS is 0 to 10, with worse disease activity represented by higher scores. [3] PASDAS low disease activity and near remission are defined as scores of  $\leq 3.2$  or  $\leq 1.9$ , respectively.[4, 5]

The mCPDAI is a validated instrument intended to assess composite psoriatic disease activity and response to therapy.[6] This instrument assesses individual domains involved, as well as the global effect of disease in all dimensions by which each patient may be affected. Domains include peripheral arthritis as assessed by the number of tender and swollen joints and the HAQ-DI, skin as assessed by the PASI and the DLQI, enthesitis as assessed by the number of sites with enthesitis and the HAQ-DI, and dactylitis as assessed by the number of digits affected and the HAQ-DI. Scores range from 0 to 12, with a higher score indicating higher disease activity.

For TJC, the number of tender and painful joints was determined by examination of 68 joints. Joints were assessed for tenderness by pressure and joint manipulation on physical examination. The patient was asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both were translated into a single tender-versus-nontender dichotomy. For SJC, the number of swollen joints was determined by examination of 66 joints. Joints were classified as either swollen or not swollen. Swelling was defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis was assessed as not swollen, unless there was unmistakable fluctuation. Dactylitis was counted as 1 swollen joint. For TJC or SJC assessments, any joints that required intra-articular injections during the study were excluded from evaluation from the time of the injection to the conclusion of the study. Missing, replaced, ankylosed, or

arthrodesed joints were identified by the investigator at screening and were excluded from evaluation during the trial.

For the patient pain VAS, patients were asked to assess the current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain. The patient pain VAS was administered prior to the TJC and SJC examinations. For the PatGA VAS, the patient's overall assessment of PsA activity was recorded using the 100-mm horizontal VAS. Patients were asked, "Considering all the ways your PsA has affected you, how do you feel your PsA is today?" where the left end represents "very well" and the right end represents "very poor." The PGA VAS was assessed by the investigator, who was required to be a physician. The investigator was asked to give an overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. Results for each of these VAS outcomes were expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick.

Enthesitis was assessed using the LEI and the SPARCC Enthesitis Index. LEI measures enthesitis at 6 sites (lateral epicondyle, left and right; medial femoral condyle, left and right; Achilles tendon insertion, left and right).[7] Each site was assigned a score of 0 (absent) or 1 (present); the results from each site were then added to produce a total score (range 0 to 6). The SPARCC Enthesitis index evaluates tenderness in a total of 16 enthesitis sites: the greater trochanter (right/left [R/L]), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L), and supraspinatus insertion (R/L).[1] Tenderness at each site was quantified on a dichotomous basis (0=nontender and 1=tender). The results from each site were then added to produce a total score (range 0 to 16).



Dactylitis was measured using the LDI-B. Once the presence of dactylitis was established in each digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot was measured.[8] Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contralateral digit. If the same digits on each hand or foot were thought to be involved, the clinician would refer to a table of normative values (provided to study sites) for a value that would be used to provide the comparison. If the ratio was  $>1.1$ , then 1 was subtracted from the calculated ratio and multiplied by 100 and the tenderness score of 0 (not tender) or 1 (tender). Otherwise, if the ratio of the circumference of the digit was  $\leq 1.1$ , then the LDI-B score was set to 0. Tenderness was assessed in the area between the joints. The results of each digit were then added to produce a total score.[9]

The PASI combined assessments of the extent of BSA involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score from 0 for no psoriasis up to 72 for the most severe disease.[10] Patients achieving PASI75, 90, or 100 were defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI compared with baseline. The sPGA was used to assess psoriasis lesions overall at a given time point. Overall lesions were categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's psoriasis was assessed at a given time point on a 6-point scale in which 0=cleared, 1=minimal, 2=mild, 3=moderate, 4=severe, and 5=very severe. Assessment of % BSA was conducted on a continuous scale from 0% to 100%, in which 1% corresponds to the size of the patients hand (including palm, fingers, and thumb).[11]

The fingernail was divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail was given a score for nail bed psoriasis (0 to 4) and nail matrix psoriasis (0 to 4) depending on the presence (1) or absence (0) of any of the features of nail psoriasis in each quadrant. The NAPSI

finger nails score of a nail is the sum of scores in nail bed and nail matrix from each quadrant (thus a maximum of 8). Each fingernail was evaluated, and the sum of all the nails is the total NAPSI finger nails score. Thus, the sum of the scores from all finger nails is 0 to 80.

The HAQ-DI is a patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities.[12, 13] The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index. The HAQ-DI minimally clinically important difference (MCID) has been estimated to be about 0.35 for patients with PsA.[14] An MCID is a clinically relevant change in a patient's status.

The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and "not relevant" responses scored as "0." Totals range from 0 to 30 (less to more impairment).

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period.[15, 16] The C-SSRS was required to be administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health Treatment of Adolescent Suicide Attempters (TASA) trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

The Self-Harm Supplement Form is a 1-question form that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form) that collects supplemental information on the self-injurious behavior was completed.

The TJC, SJC, BSA, and C-SSRS were assessed at screening, baseline, and post-baseline visits from week 4 to 52. The patient pain VAS, PatGA VAS, PGA VAS, LEI, SPARCC Enthesitis Index, PASI, HAQ-DI, and DLQI were assessed at baseline and post-baseline visits from week 4 to 52. LDI-B and NAPSI fingernails were assessed at baseline and each post-baseline visit from week 12 to 52. The sPGA was assessed at the baseline visit only. Blinded assessors evaluated the TJC, SJC, LEI, SPARCC Enthesitis Index, PASI, sPGA, BSA, and NAPSI fingernails.

#### **Adjudication of Cerebrocardiovascular Events and Suspected Inflammatory Bowel Disease**

Data on cerebrocardiovascular events were adjudicated by an external Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist. Data on suspected inflammatory bowel disease (IBD), as identified by events possibly indicative of ulcerative colitis and Crohn's disease, were adjudicated by an external CEC made up of gastroenterologists with expertise in IBD according to the EPIdemiologie des Maladies de l'Appareil Digestif (EPIMAD) criteria for adjudication of suspected IBD.[17] The role of the CEC was to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of the study.

#### **STATISTICAL ANALYSIS CONSIDERATIONS FOR THE PRIMARY OUTCOME MEASURE**

After the week 24 database lock and the initial run of the analyses, a data scenario reflecting a medical inconsistency was identified. Per inclusion criteria, patients must have had active psoriasis involvement with BSA  $\geq 3\%$ . Nine patients were found to have PASI=0 at baseline, although each patient met the

entry criteria of BSA  $\geq 3\%$ . This scenario was not explicitly described in the protocol and statistical analysis plan and therefore was not anticipated in the statistical coding; the standard programming codes were followed. Due to the denominator (ie, baseline PASI score) being 0, the percent improvement from baseline for PASI was not calculated for these 9 patients, and these 9 patients were labeled as “nonresponders” for PASI 75/90/100. The labeling of patients as nonresponders occurred before the sponsor became aware of the data issue (ie, 9 patients with baseline PASI=0).

Using the PASI and BSA study data from these patients, as well as medical judgment, it was established that these 9 patients were eligible patients who met the inclusion criteria per protocol (ie, active Ps with BSA  $\geq 3\%$ ). Therefore, the inclusion of these patients in the study was appropriate and aligned with the protocol.

Additionally, the longitudinal data were examined and provided evidence of clinical response for those patients who started with PASI=0 and BSA  $\geq 3\%$  at baseline and achieved both PASI=0 and BSA=0 at post-baseline visits.

The following approaches were used to address the data scenario for these 9 patients:

- Primary Analysis
  - A patient with baseline PASI=0 and baseline BSA  $\geq 3\%$  was considered a post-baseline PASI 100 responder if, and only if, PASI=0 and BSA=0 at the same postbaseline visit. PASI100 responders are also considered responders to PASI75 and 90.
- Sensitivity Analyses
  - Regardless of the BSA outcome, any patient with baseline PASI=0 and post-baseline PASI=0 was considered a PASI100 responder. If a patient with baseline PASI=0 had a post-baseline PASI  $>0$ , the patient was considered a nonresponder for that specific post-baseline visit.

- This approach used only PASI data when considering PASI response.
- Regardless if data were available, any patient with baseline PASI=0 was excluded from the analysis.
  - This approach assumed that the 9 patients were not eligible for inclusion in the study because baseline PASI=0 was not expected, thus also questioning the validity of the baseline BSA data. This approach draws the study conclusion based on evidence of those patients without data inconsistency at baseline, which is 98.4% of the entire study population.
- Additional Analysis
  - Regardless of the post-baseline outcome, any patient with baseline PASI=0 was considered a “nonresponder.”
    - This approach lacked medical and statistical support because it predetermined the response status of these 9 patients purely based on their baseline data even before they were allocated to any treatment.
    - This analysis produced the same results as the initial programming run, in which the standard program coding labeled the patients with baseline PASI=0 as nonresponders.

Results from these analyses are included in online supplementary Table S1. Results from the 2 sensitivity analyses at week 24 were consistent with the results of the primary analysis at week 24. The additional analysis resulted in a treatment difference that was not statistically significant. Given these observations and the totality of evidence of the study, the primary objective of the study was achieved.

## **SUPPLEMENTARY STATISTICAL METHODOLOGY**

### **Sample Size Determination**

#### Primary Endpoint (simultaneous ACR50 and PASI100)

Sample size was calculated assuming 31.3% and 13.6% of patients in the IXE and ADA treatment groups, respectively, would simultaneously achieve ACR50 and PASI100, as observed in the csDMARD-experienced population from the SPIRIT-P1 study (ClinicalTrials.gov: NCT01695239). According to nQuery software, a total sample size of 550 (ie, 275 patients per treatment group) using a 2-sided Fisher's exact test at 0.05 level of significance would yield approximately 99% power for testing IXE vs ADA.

#### Major secondary endpoint 1 (ACR50)

For testing the noninferiority of IXE to ADA for ACR50 response, assumed ACR50 response rates were 43.8% and 44.1% for the IXE and ADA treatment groups, respectively, as observed in the csDMARD-experienced population from the SPIRIT-P1 study. The sample size of 550 (as determined for the primary endpoint) would yield 78% power at a 1-sided 0.025 level of significance based on a noninferiority margin of -12%.

#### Major secondary endpoint 2 (PASI100)

For testing superiority of IXE to ADA for PASI 100 response, assumed PASI100 response rates were 46.9% and 23.7%, as observed for IXE and ADA in the csDMARD experienced population from the SPIRIT-P1 study. The sample size of 550 (as determined for the primary endpoint) would yield approximately 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

#### **Multiple Testing Procedure**

The primary and major secondary endpoints were sequentially tested in the following order to compare IXE vs ADA:

1. Test 1 for primary endpoint: Proportion of patients simultaneously achieving ACR50 and PASI100 at week 24.
  - a. A superiority test of the primary endpoint was performed at an overall 2-sided  $\alpha=0.05$ .
2. Test 2 for major secondary endpoint #1: Proportion of patients achieving ACR50 at week 24
  - a. If the test for the primary endpoint was significant, then a noninferiority test for the major secondary endpoint #1 was performed.
3. Test 3 for major secondary endpoint #2: Proportion of patients achieving PASI100 at week 24
  - a. If the test for major secondary endpoint #1 was significant, then a superiority test for major secondary endpoint #2 was performed.

If a test in this sequence was not significant, all subsequent tests were considered nonsignificant. There was no adjustment for multiple comparisons for any other analyses.

### **Noninferiority Testing**

For assessing noninferiority of IXE to ADA, missing data were imputed using the nonresponders imputation (NRI) method. Noninferiority analysis was performed on the intent-to-treat (ITT) population using a prespecified fixed margin approach. There is no universally accepted value for what is considered to be a clinically unimportant difference between 2 treatments for a particular efficacy measure. Points to consider from European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) and Food and Drug Administration (FDA) guidance state that an appropriate noninferiority margin should be based on both clinical and statistical grounds.[18, 19]

The null hypothesis was rejected if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in proportions of responders on IXE minus ADA is greater than the prespecified margin, meaning IXE will be deemed noninferior to ADA. If the lower bound of the CI exceeds 0 (the corresponding p-value from the logistic regression model will also be produced), IXE will be deemed

superior to ADA based on the p-value. The 95% CIs for the difference in proportions will be calculated using the simple asymptotic method, without continuity correction (ie, normal approximation to the binomial distribution).

Based on EMEA CHMP, FDA guidance, and Weinblatt et al., a noninferiority margin of -12.0% for ACR50 between IXE and ADA (ie, response rate of IXE – response rate of ADA) is considered appropriate.[18-20] This noninferiority margin represents an approximately 50% preservation of the ADA treatment effect (based on the difference between ADA and placebo) observed in a historical Phase III study for ADA 40 mg twice weekly compared with placebo (ADEPT study) and the SPIRIT-P1 study of IXE where ADA was used as an active reference arm in patients with active PsA.[21, 22]

#### **Additional Details on Statistical Analyses**

Analyses were performed at the time (cutoff date) when the last patient completed the week 24 visit, early termination visit, or discontinued from the open-label treatment period. This database lock included all data collected by the cutoff date, including data after week 24. This database lock at week 24 was the primary database lock for the study, and all primary and major secondary study objectives were assessed at this time. A final database lock will occur after all enrolled patients have completed or discontinued the post-treatment follow-up period.

Mixed effects model of repeated measures analyses of continuous efficacy measures were conducted using a restricted maximum likelihood-based repeated measures approach. The covariance structure to model the within-patient errors was unstructured. Type III tests for the least squares means were used for the statistical comparison. Missing data were imputed using a modified baseline observation carried forward method. For patients discontinuing investigational product due to an adverse event, including death, the baseline observation was carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last non-missing



post-baseline observation before discontinuation was carried forward to the corresponding time point of evaluation. Randomized patients without at least 1 post-baseline observation were not included for evaluation, with the exception of patients discontinuing study treatment due to an adverse event (including death).

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## SUPPLEMENTARY TABLES

<b>Online supplementary Table S1. Simultaneous achievement of ACR50 and PASI100 at week 24 as determined by primary, sensitivity, and additional analysis methodology (NRI)</b>				
	<b>ADA (N=283)</b>	<b>IXE (N=283)</b>	<b>Treatment difference 95% CI</b>	<b>p-value (IXE vs ADA)</b>
Primary analysis <sup>a</sup>	79/283 (28) 22.7% to 33.1%	102/283 (36) 30.4% to 41.6%	8.1% 0.5% to 15.8%	0.036
Sensitivity analysis 1 <sup>b</sup>	79/283 (28) 22.7% to 33.1%	102/283 (36) 30.4% to 41.6%	8.1% 0.5% to 15.8%	0.036
Sensitivity analysis 2 <sup>c</sup>	78/280 (28) 22.6% to 33.1%	99/277 (36) 30.1% to 41.4%	7.9% 0.2% to 15.6%	0.043
Additional analysis <sup>d</sup>	78/283 (28) 22.4% to 32.8%	99/283 (35) 29.4% to 40.5%	7.4% -0.2% to 15.0%	0.054

ACR, American College of Rheumatology; ADA, adalimumab; BSA, body surface area; CI: confidence interval; IXE, ixekizumab; NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index.

Values presented as n/N (%), 95% CIs.

<sup>a</sup>A patient with baseline PASI=0 and baseline BSA  $\geq$ 3% was considered a postbaseline PASI100 responder if, and only if, PASI=0 and BSA=0 at the same post-baseline visit. PASI100 responders are also considered responders to PASI75 and 90.

<sup>b</sup>Regardless of the BSA outcome, any patient with baseline PASI=0 and post-baseline PASI=0 was considered a PASI100 responder. If a patient with baseline PASI=0 had a postbaseline PASI >0, the patient was considered a nonresponder for that specific post-baseline visit.

<sup>c</sup>Regardless if data were available, any patient with baseline PASI=0 was excluded from the analysis.

<sup>d</sup>Regardless of the postbaseline outcome, any patient with baseline PASI=0 was considered a nonresponder.

Online supplementary Table S2. Summary of outcome measures.	
Outcome measure	Description
ACR50 + PASI100	The proportion of patients simultaneously achieving ACR50 and PASI100.
ACR20/50/70	Improvement from baseline of $\geq 20\%$ , $\geq 50\%$ , or $\geq 70\%$ in TJC, SJC, and at least 3 of the 5 ACR Core Set criteria
TJC	The number of tender and painful joints, determined by physical examination of 68 joints.
SJC	The number of swollen joints determined by physical examination of 66 joints.
ACR core set criteria	
Patient pain VAS,	A patient-reported assessment of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain.
PatGA VAS	A patient reported assessment of PsA activity by marking a vertical tick on a 100-mm horizontal VAS. Patients were asked, "Considering all the ways your PsA has affected you, how do you feel your PsA is today?" where the left end represents "very well" and the right end represents "very poor."
PGA VAS	A physician-reported assessment where the investigator is asked to give an overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease.
HAQ-DI	A patient-reported questionnaire to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities. The disability section scores the degree of difficulty (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do), covering the 8 domains. Scores for each of the functional domains are averaged to calculate the functional disability index. A minimally clinically important difference is estimated to be about 0.35 for patients with PsA.
CRP	A measure of acute-phase reactant measured in mg/L
PASI	An assessment of psoriasis severity that combines the extent of BSA involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation

	(scaling), erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score from 0 for no psoriasis up to 72 for the most severe disease. PASI75, 90, or 100 are defined an improvement from baseline of $\geq 75\%$ , 90%, or 100%, respectively.
MDA and VLDA	Achievement of either 5 (MDA) or 7 (VLDA) of the 7 MDA components including TJC $\leq 1$ ; SJC $\leq 1$ ; PASI total score $\leq 1$ or BSA $\leq 3$ ; patient pain VAS score $\leq 15$ ; PatGA VAS score $\leq 20$ ; HAQ-DI score $\leq 0.5$ ; and tender enthesal points $\leq 1$
DAPSA	A composite measure that includes TJC and SJC, PatGA VAS, patient pain VAS, and CRP. Higher scores reflect more severe disease activity. DAPSA remission: $\leq 4$ . DAPSA low disease activity or remission: $\leq 14$ .
PASDAS	A weighted index comprising assessments of joints, function, acute phase response, quality of life, PGA VAS, and PatGA VAS. The score range of the PASDAS is 0 to 10, with worse disease activity represented by higher scores. PASDAS low disease activity: $\leq 3.2$ . PASDAS near remission: $\leq 1.9$ .
mCPDAI	A composite measure that assesses individual domains and global effect of PsA. Domains include peripheral arthritis, skin, enthesitis, and dactylitis. Scores range from 0 to 12, with a higher score indicating higher disease activity.
SPARCC Enthesitis index	An evaluation of tenderness in 16 enthesitis sites, quantified on a dichotomous basis (0=nontender and 1=tender). The results from each site are added to produce a total score (range 0 to 16).
LEI	A measure of enthesitis assessed at 6 sites, assigned a score of 0 (absent) or 1 (present). The results from each site were then added to produce a total score (range 0 to 6).
LDI-B	For each digit with dactylitis, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured. If the same digits on each hand or foot are thought to be involved, the clinician refers to a table of normative values for a value that would be used to provide the comparison. If the ratio is $>1.1$ , then 1 is subtracted from the calculated ratio and multiplied by 100 and the tenderness score of 0 (not tender) or 1 (tender). If the ratio of the circumference of the digit is $\leq 1.1$ , then the LDI-B score is set to 0. The results of each digit are added to produce a total score.
NAPSI fingernails	An assessment of fingernail psoriasis severity where the fingernail is divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail is given a score for nail bed psoriasis (0 to 4) and nail matrix psoriasis (0 to 4) depending on the presence (1) or absence (0) of any of the features of nail psoriasis in each quadrant. The NAPSI fingernails score of a nail is the sum of scores in nail bed and

	nail matrix from each quadrant (thus a maximum of 8). The total score is the sum of scores for each fingernail (range of 0 to 80).
DLQI	A patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include “not at all,” “a little,” “a lot,” and “very much,” with corresponding scores of 0, 1, 2, and 3, respectively, and “not relevant” responses scored as “0.” Totals range from 0 to 30 (less to more impairment).
sPGA	A measure of overall psoriasis severity. Lesions are categorized by descriptions for induration, erythema, and scaling. The patient’s psoriasis is assessed at a given time point on a 6-point scale in which 0=cleared, 1=minimal, 2=mild, 3=moderate, 4=severe, and 5=very severe.
% BSA	A measure of psoriasis body surface area involvement conducted on a continuous scale from 0% to 100%, in which 1% corresponds to the size of the patients hand (including palm, fingers, and thumb).
<p>ACR, American College of Rheumatology; BSA, body surface area; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; HAQ-DI, Health Assessment Questionnaire–Disability Index; LDI-B, Leeds Dactylitis Index–Basic; LEI, Leeds Enthesitis Index; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; NAPSI, Nail Psoriasis Area and Severity Index; PASDAS, psoriatic arthritis disease activity score; PASI, Psoriasis Area and Severity Index; PatGA, patient’s global assessment of disease activity; PGA, physician’s global assessment of disease activity; PsA, psoriatic arthritis; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; sPGA, static physician’s global assessment; TJC, tender joint count, VAS, visual analog scale; VLDA, very low disease activity.</p>	

<b>Online supplementary Table 3. List of serious infections</b>	
<b>ADA</b>	<b>IXE</b>
<b>N=283</b>	<b>N=283</b>
Appendicitis, n=1	Appendicitis, n=1
Cellulitis, n=1	Cellulitis, n=1
Abscess, n=1	Arthritis bacterial, n=1
Lower respiratory tract infection, n=1	Infections colitis, n=1

Lymph node tuberculosis, n=1	
Meningitis viral, n=1	
Pneumonia legionella, n=1	
Pyelonephritis, n=1	
Sepsis, n=1	
ADA, adalimumab; IXE, ixekizumab.	